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Catalytic Asymmetric Synthesis of Piperidines from Pyrrolidine: Concise Synthesis of L-733,060§

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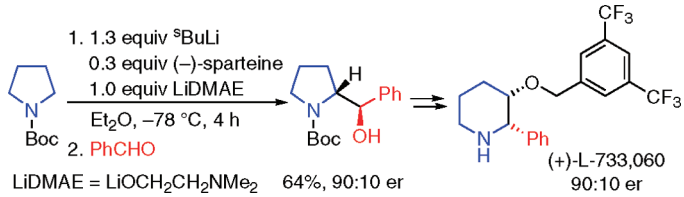
ABSTRACT



Catalytic asymmetric deprotonation-aldehyde trapping-ring expansion from a 5- to a 6-ring delivers a concise route to each stereoisomer of *β*-hydroxy piperidines starting from *N*-Boc pyrrolidine. The methodology is utilized in a 5-step catalytic asymmetric synthesis of the neurokinin-1 receptor antagonist, (+)-L-733,060.

Chiral piperidines are widespread in natural products and are common subunits in pharmaceutical lead compounds. One important class of biologically active piperidine contains the *β*-hydroxy piperidine motif. Selected examples are (−)-swainsonine, an inhibitor of lysosomal α-mannosidase and mannosidase II and a potential anticancer drug,[1] (+)-febrifugine, an antimalarial agent,[2] and (+)-L-733,060, a potent and selective neuronkinin-1 substance P receptor antagonist[3] (Figure 1). Although the synthesis of these *β*-hydroxy piperidines has attracted recent attention,[4−6] many of the synthetic approaches are lengthy and not sufficiently flexible to allow stereoselective access to the different enantiomeric and diastereomeric structures required. To address this, we have developed a new and general strategy for the stereoselective synthesis of each stereoisomer of chiral *β*-hydroxy piperidines.

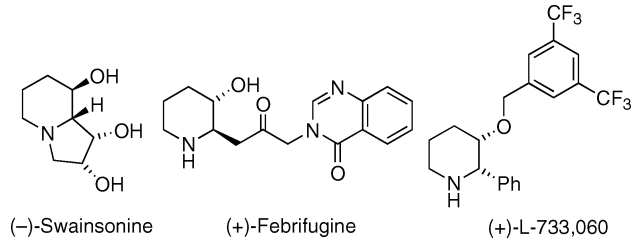


Figure 1. Biologically active *β*-hydroxy piperidines.

§ Dedicated to Professor R. J. K. Taylor on the occasion of his 60th birthday.

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(1) (a) Liao, Y. F.; Lal, A.; Moremen, K. W. *J. Biol. Chem.* **1996**, *271*, 28348. (b) Elbein, A. D.; Solf, R.; Dorling, P. R.; Vosbeck, K. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 7393. (c) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer. Res.* **1995**, *1*, 935.

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(4) For the most recent syntheses of (−)-swainsonine, see: (a) Shi, G.-F.; Li, J.-Q.; Jiang, X.-P.; Cheng, Y. *Tetrahedron* **2008**, *64*, 5005. (b) Sharma, P. K.; Shah, R. N.; Carver, J. P. *Org. Process Res Dev.* **2008**, *12*, 831. (c) Guo, H.; O'Doherty, G. *Tetrahedron* **2008**, *64*, 304. (d) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Tetrahedron* **2007**, *63*, 9082. (e) Ceccon, J.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2006**, *8*, 4739.

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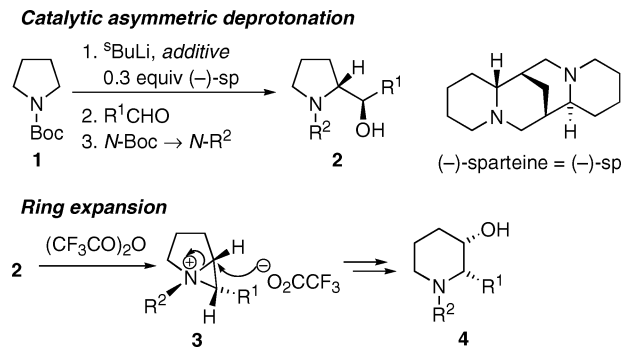
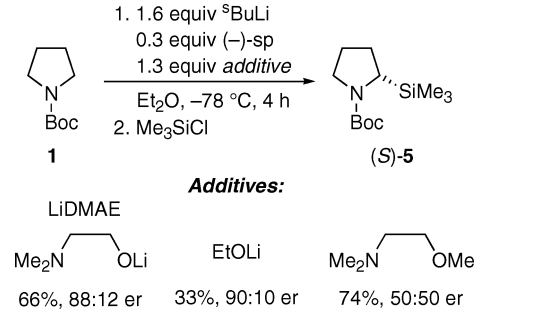
Scheme 1



Our approach to β-hydroxy piperidines **4** (Scheme 1) comprises two key steps: (i) catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1** using *s*-BuLi and substoichiometric amounts of (−)-sparteine (in the presence of a stoichiometric achiral additive) and subsequent trapping with an aldehyde to give amino alcohols **2**; (ii) ring expansion of amino alcohols **2** to the corresponding β-hydroxy piperidines **4** via formation and ring-opening of an intermediate aziridinium ion **3** (R^2 = alkyl).[7−9] Scheme 1 depicts the synthesis of β-hydroxy piperidines **4** with (2*S*,3*S*) stereochemistry; other stereoisomers of **4** would be available by changing the chiral ligand (e.g., to a (+)-sparteine surrogate[10]) and/or the diastereoselectivity of the addition to the aldehyde. In this paper, we report a new method for the catalytic asymmetric deprotonation step using a commercially available achiral additive, implementation of the deprotonation-trapping-ring expansion strategy for the synthesis of β-hydroxy piperidines **4** and a transmetalation approach to allow selective access to each diastereomer. Ultimately, we exemplify our methodology with a five-step catalytic asymmetric synthesis of (+)-L-733,060, which is half the length of the previous syntheses.[6]

We have previously reported a catalytic asymmetric protocol for the Beak-style[11] deprotonation of *N*-Boc pyrrolidine **1** using *s*-BuLi in tandem with 0.1−0.3 equiv of (−)-sparteine.[12] The approach is only successful if a stoichiometric amount of an additive is included to recycle and turnover the (−)-sparteine. The optimum additive, a bis-*i*-Pr-bispidine, is not commercially available and cannot be separated from the chiral ligand after use (thus precluding reuse of the chiral ligand). To address these two important limitations, we screened a range of commercially available additives and ultimately discovered that lithiated dimethylaminoethanol (LiDMAE[13]) worked well. Thus, lithiation of *N*-Boc pyrrolidine **1** using 1.6 equiv of *s*-BuLi, 0.3 equiv of (−)-sparteine and 1.3 equiv of LiDMAE (formed *in situ* by lithiation of DMAE using an extra equivalent of *s*-BuLi) and subsequent reaction with Me_3SiCl delivered a 66% yield of adduct (*S*)-**5** of 88:12 er (Scheme 2). Notably, the (−)-sparteine

Scheme 2



can be easily separated from the DMAE since the DMAE can be extracted into $NaOH_{(aq)}$.[14] This means that the chiral ligand can be recovered and reused.

We verified that it is necessary to have both the lithium alkoxide *and* the dimethylamino group in the additive: use of lithium ethoxide gave (*S*)-**5** in 90:10 er but in only 33% yield, indicating that there was no turnover of (−)-sparteine and use of *N*,*N*-dimethyl-2-methoxyethylamine gave *rac*-**5** (74% yield), reflecting a fast background deprotonation by the *s*-BuLi/amino ether complex (Scheme 2). Next, with a view to optimizing

(5) For syntheses of (+)-febrifugine, see: (a) Sieng, B.; Lozano Ventura, O.; Bellosta, V.; Cossy, J. *Synlett* **2008**, 1216. (b) Ashoorzadeh, A.; Caprio, V. *Synlett* **2005**, 346. (c) Katoh, M.; Matsune, R.; Nagase, H.; Honda, T. *Tetrahedron Lett.* **2004**, *45*, 6221. (d) Huang, P.-Q.; Wei, B.-G.; Ruan, Y.-P. *Synlett* **2003**, 1663. (e) Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2001**, *3*, 953. (f) Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193. (g) Takeuchi, Y.; Azuma, K.; Takakura, K.; Abe, H.; Harayama, T. *Chem. Commun.* **2000**, 1643. (h) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175.

(6) For syntheses of (+)-L-733,060, see: (a) Liu, R.-H.; Fang, K.; Wang, B.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2008**, *73*, 3307. (b) Emmanuvel, L.; Sudalai, A. *Tetrahedron Lett.* **2008**, *49*, 5736. (c) Cherian, S. K.; Kumar, P. *Tetrahedron: Asymmetry* **2007**, *18*, 982. (d) Oshitari, T.; Mandai, T. *Synlett* **2006**, 3395. (e) Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3579. (f) Yoon, Y.-J.; Joo, J.-E.; Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Tetrahedron Lett.* **2005**, *46*, 739. (g) Huang, P.-Q.; Liu, L.-X.; Wei, B.-G.; Ruan, Y.-P. *Org. Lett.* **2003**, *5*, 1927. (h) Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915. For synthesis of (−)-L-733,060, see: (i) Takahashi, K.; Nakano, H.; Fujita, R. *Tetrahedron Lett.* **2005**, *46*, 8927.

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(9) For selected examples, see: (a) Calvez, O.; Chiaroni, A.; Langlois, N. *Tetrahedron Lett.* **1998**, *39*, 9447. (b) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Eur. J. Org. Chem.* **1999**, 1693. (c) Cossy, J.; Mirguet, O.; Gomez Pardo, D.; Desmurs, J.-R. *Tetrahedron Lett.* **2001**, *42*, 5705. (d) Lee, J.; Hoang, T.; Lewis, S.; Weissm an, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223. (e) Dechamps, I.; Gomez Pardo, D.; Cossy, J. *Synlett* **2007**, 263. (f) Drouillat, B.; Couty, F.; David, O.; Evano, G.; Marrot, J. *Synlett* **2008**, 1345. (g) Durrat, F; Vargas Sanchez, M.; Couty, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2008**, 3286.

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(12) (a) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378. (b) McGrath, M. J.; Bilke, J. L.; O'Brien, P. *Chem. Commun.* **2006**, 2607. (c) Bilke, J. L.; O'Brien, P. *J. Org. Chem.* **2008**, *73*, 6452.

(13) For selected examples on the use of *n*-BuLi/LiDMAE in pyridine lithiation, see: (a) Gros, P.; Fort, Y.; Queguiner, G.; Caubère, P. *Tetrahedron Lett.* **1995**, *36*, 4791. (b) Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3071. (c) Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375. (d) Gros, P. C.; Doudouh, A.; Woltermann, C. *Chem. Commun.* **2006**, 2673.

(14) A solution of (−)-sparteine (10.0 mmol) and DMAE (33.3 mmol) in Et_2O (35 mL) was washed with 20% w/v $NaOH_{(aq)}$ solution (6 × 50 mL). Then, the Et_2O layer was dried (Na_2SO_4) and evaporated under reduced pressure to give pure (−)-sparteine (^1H NMR spectroscopy).

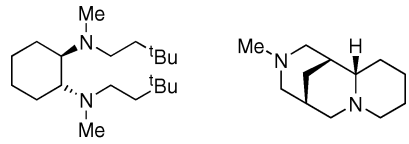


Figure 2. Chiral diamines.

the catalytic deprotonation conditions, we varied the stoichiometry of the chiral ligand/LiDMAE and investigated the use of other chiral ligands ((−)-sparteine surrogate **6**[15] and (+)-sparteine surrogate **7**,[10] Figure 2) (Table 1 and Scheme 2).

Table 1. Optimisation of the Catalytic Asymmetric Deprotonation Using Lithiated Dimethylaminoethanol (LiDMAE) for the Conversion of *N*-Boc Pyrrolidine **1** into Adduct (*S*)- or (*R*)-**5**

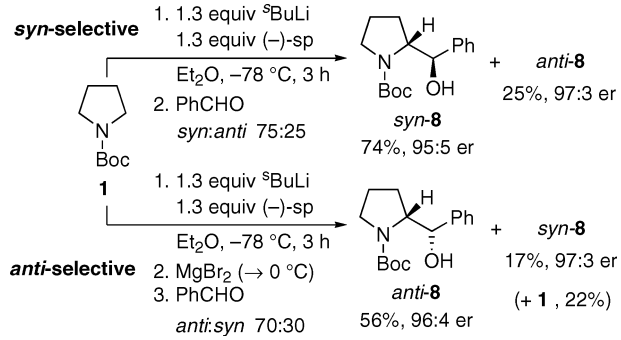
entry	equiv[a] *s*-BuLi	equiv chiral ligand	equiv[b] Li DMAE	yield (%)[c]	er[d] *S*:*R*
1	1.3	0	1.3	4	–
2	2.6	1.3, (−)-sp	1.3	62	98:2
3	1.6	0.3, (−)-sp	1.3	66	88:12
4	1.6	0.3, **6**	1.3	60	93:7
5	1.6	0.3, **7**	1.3	70	11:89
6	1.4	0.2, (−)-sp	1.2	53	88:12
7	1.4	0.2,**7**	1.2	74	13:87
8	1.3	0.1, (−)-sp	1.2	58	88:12
9	1.3	0.1, **7**	1.2	43	2:98
10	1.25	0.05, (−)-sp	1.2	36	77:23
11	1.3	0.3, (−)-sp	1.0	58	97:3
12	1.3	0.3, **7**	1.0	74	8:92

[a] Amount of *s*-BuLi available after formation of LiDMAE. [b] Amount of LiDMAE formed by premixing DMAE and *s*-BuLi. [c] Yield of adduct **5** after purification by column chromatography. [d] Er determined using chiral GC.

First, we showed that there was no appreciable background deprotonation of *N*-Boc pyrrolidine **1** using *s*-BuLi in the presence of LiDMAE: a 4% yield of *rac*-**5** was obtained (entry 1). We also showed that lithiation using *s*-BuLi/(−)-sparteine and stoichiometric LiDMAE gave adduct (*S*)-**5** in high enantioselectivity (62% yield, 98:2 er, entry 2). Use of 0.3, 0.2, or 0.1 equiv of (−)-sparteine all gave 88:12 er (entries 3, 6 and 8) but use of 0.05 equiv of (−)-sparteine led to poor turnover (36% yield) and lower enantioselectivity (77:23 er) (entry 10). Using 0.3 equiv of (−)-sparteine surrogate **6** worked especially well: (*S*)-**5** of 93:7 er was produced in 70% yield (entry 4). The opposite enantiomeric series could be accessed with similar enantioselectivity (87:13−92:8 er) using the (+)-sparteine surrogate **7** (entries 5, 7 and 9). Finally, our optimum lithiation conditions involved using 1.3 equiv of *s*-BuLi, 0.3 equiv of chiral ligand and 1.0 equiv of LiDMAE: use of (−)-sparteine gave (*S*)-**5** in 97:3 er (entry 11) whereas use of (+)-sparteine surrogate **7** gave (*R*)-**5** in 92:8 er (entry 12). We believe that the success of the catalytic asymmetric deprotonation using LiDMAE results from a negligible background rate of deprotonation by *s*-BuLi/LiDMAE (entry 1) and a ligand exchange process (where the LiDMAE can displace the chiral ligand from the lithiated *N*-Boc pyrrolidine to allow recycling of the chiral ligand).

With an efficient catalytic asymmetric deprotonation protocol in place, our attention then focused on the stereoselectivity of the addition of the organolithium to the aldehyde[16] and subsequent ring expansion to the piperidines. Our intention was to identify a simple way of accessing each diastereomeric hydroxy piperidine and, for the initial studies, we used stoichiometric *s*-BuLi and (−)-sparteine for the deprotonation of *N*-Boc pyrrolidine **1**. Direct trapping of the lithiated *N*-Boc pyrrolidine with benzaldehyde was *syn*-selective, delivering a 75:25 mixture of alcohols *syn*- and *anti*-**8** from which the major diastereomer, *syn*-**8** (95:5 er), was obtained in 74% yield after chromatography (Scheme 3). The relative stereochemistry was assigned by X-ray crystallography of alcohol *anti*-**8**.[17]

Scheme 3



We reasoned that different stereoselectivity could be obtained using other metalated *N*-Boc pyrrolidines. Indeed, transmetalation of lithiated *N*-Boc pyrrolidine to the corresponding Grignard reagent using $MgBr_2$[18,19] and then addition to benzaldehyde gave a reversal in stereoselectivity: a 70:30 mixture of *anti*- and *syn*-**8** was formed. In this way, alcohol *anti*-**8** (96:4 er) was obtained in 56% yield (Scheme 3). It is notable that there is no loss of er during the transmetalation of Li to Mg despite the fact that the reaction mixture was stirred at 0 °C for 30 min. Clearly, the Grignard reagent has a significantly higher barrier to enantiomerization than the corresponding organolithium reagent.[20,21]

Although the ring expansion of a 2-chloromethylpyrrolidine to a 3-chloropiperidine was first described by Fuson and Zirkle

(15) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.

(16) We are aware of only one example of the addition of a lithiated *N*-Boc pyrrolidine to an aldehyde: Majewski, M.; Shao, J.; Nelson, K.; Nowak, P.; Irvine, N. M. *Tetrahedron Lett.* **1998**, *39*, 6787.

(17) CCDC 696161 (*anti*-**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at http://www.ccdc.cam.ac.uk/data_request/cif.

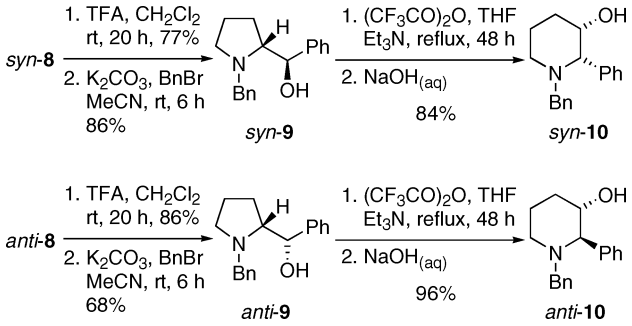
(18) Kise, N.; Urai, T.; Yoshida, J.-i. *Tetrahedron: Asymmetry* **1998**, *9*, 3125.

(19) Zhang, P.; Gawley, R. E. *Tetrahedron Lett.* **1992**, *33*, 2945.

(20) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716.

in 1948,[7] it was not until 1995 that Cossy reported a useful method for converting 2-hydroxymethyl pyrrolidines into β-hydroxy piperidines;[8] subsequently, a range of synthetic applications have appeared.[4d,9] Such a ring expansion is only possible if the nitrogen lone pair is available to participate in aziridinium ion formation. As a result, we needed to transform the *N*-Boc group into an *N*-alkyl substituent. This was readily achieved by treating alcohols *syn*-**8** and *anti*-**8** with TFA and then benzyl bromide to give *syn*-**9** and *anti*-**9** (Scheme 4). Cossy's conditions for ring expansion

Scheme 4



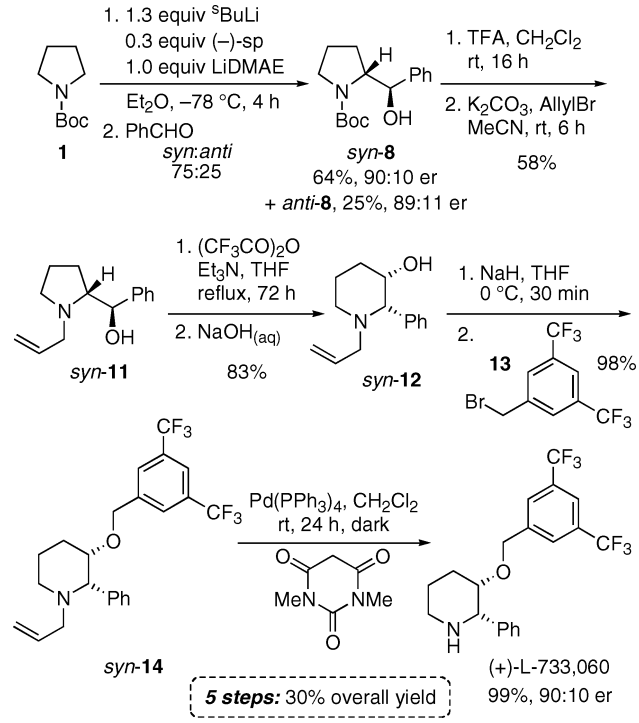
((CF$_3$CO)$_2$O, THF, Et$_3$N, reflux, 48 h and then base-mediated ester hydrolysis) were successful with both *syn*- and *anti*-**9** giving piperidines *syn*-**10** (84% yield) and *anti*-**10** (96% yield) respectively (Scheme 4). The high yield obtained for both of these reactions is notable since it has previously been reported that the *N*-Me version of *syn*-**9** did not undergo the ring expansion.[9b]

Finally, to validate the synthetic utility of the deprotonation-trapping-ring expansion methodology, we chose (+)-L-733,060 as a suitable target since it has important biological activity and previous syntheses are ≥10 steps.[6] First, we carried out the catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1** using the optimized conditions (1.3 equiv of *s*-BuLi, 0.3 equiv of (−)-sparteine and 1.0 equiv of LiDMAE) and then trapped the organolithium reagent with benzaldehyde. The stereoselectivity (*syn*:*anti* = 75:25) was the same as the stoichiometric version and, after chromatography, alcohol *syn*-**8** of 90:10 er was obtained in 64% yield; alcohol *anti*-**8** (25% yield, 89:11 er) was also isolated (Scheme 5).

Alcohol *syn*-**8** was converted into *N*-allylated alcohol *syn*-**11** (58% yield) via Boc deprotection and allylation (Scheme 5) since we needed an *N*-alkyl protecting group that could be cleaved in the presence of the benzylic ether present in (+)-L-733,060. Then, alcohol *syn*-**11** was ring-expanded (using (CF$_3$CO)$_2$O and subsequent base-mediated ester hydrolysis) to piperidine *syn*-**14** (83% yield). The remaining two steps proceeded uneventfully and in high yield. *O*-Benzylation of *syn*-**12** was achieved by NaH deprotonation and alkylation with

(21) For a similar effect with *O*-alkyl carbamates, see: Tomooka, K.; Shimizu, H.; Nakai, T. *J. Organomet. Chem.* **2001**, *624*, 364.

Scheme 5



functionalized benzyl bromide **13**. Finally, treatment of *syn*-**14** with Pd(0) and *N*,*N*′-dimethylbarbituric acid led to smooth *N*-deallylation to give (+)-L-733,060 of 90:10 er (by chiral shift NMR spectroscopy in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) which exhibited $[\alpha]_D$ +55.0 (*c* 1.0 in CHCl$_3$) [lit.,[6a] $[\alpha]_D$ +73.9 (*c* 0.64 in CHCl$_3$)]. Our synthesis of (+)-L-733,060 is five steps and proceeds in 30% overall yield, making it the shortest synthesis to date.

In summary, we report a new two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1** utilizing a stoichiometric additive that is commercially available and can be separated from the chiral ligand. This protocol is combined with aldehyde trapping and pyrrolidine → piperidine ring expansion to selectively deliver chiral β-hydroxy piperidines such as *syn*-**10** or *anti*-**10** in just four steps. Either enantiomer of these compounds can be accessed using (−)-sparteine or (+)-sparteine surrogate **7** in the deprotonation step. The methodology provides a concise entry to β-hydroxy piperidines as illustrated with a five-step synthesis of (+)-L-733,060.

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Supporting Information Available: Full experimental procedures, characterization data and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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